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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/737,457	03/12/97	CARDY D	960670.ORI

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EXAMINER	
LUBET, M	
ART UNIT	**PAPER NUMBER**
1644	8

DATE MAILED: 08/04/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary

Application No.	Applicant(s)
08/737,457	Cardy et al.
Examiner	**Group Art Unit**
Lubet	1644

☒ Responsive to communication(s) filed on *Jan 23, 1998*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-23* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-23* is/are rejected.

☒ Claim(s) *1-23* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4,5*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Technology Group 1600 Group 1640 Art Unit 1644.

Claims 1-23 are pending and are generic to a plurality of disclosed patentably distinct species comprising: a chimeric receptor comprising a plurality of patentably distinct a)1 binding portion, 2)an effector portion and optionally 3)a translocation portion and/or 4) a signal portion Applicant is required to elected a single embodiment of the elected invention. .

I) Applicant is required to select a binding portion with binding affinity for a particular target cell component.

ii) Applicant is required to select a target cells in which the chimeric protein is expressed selected from the group consisting of, APC, aberrant, diseased or virus infected cell.

iii) Applicant is required to select an effector portion selected from the group consisting of MAGE 1, 2 or 3 antigens, tetanus toxin P2 peptide, HIV-V3 loop region , p53, influenza virus matrix protein or influenza nucleoprotein.

iv) Applicant is required to select translocation portion selected from the group consisting of bacterial exotoxin, HIV tat protein or endosome-disrupting function of an adenovirus.

v)Applicant is required to select a signal portion, IE Pseudomonas exotoxin or a chimeric without a signal portion.

Applicant is required, in reply to this action, to elect a single embodiment of the invention to which the claims shall be restricted if no generic claim is finally held to be allowable. For instance, Applicant could elect a chimeric protein comprising

I) an anti-MHC immunoglobulin molecule expressed on APC cells

ii) p53 protein

iii) translocation domain of HIV tat protein

iv) and signal portion derived from translocation domain of Pseudomonas exotoxin.

The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: The special technical feature of each embodiment is the structural (amino acid sequence) and functional characteristic of the particular chimeric

polypeptide. Chimeric polypeptides having different binding portions and different effector portions differ in the biochemical and functional characteristics.

During a telephone conversation with Orrin Haugen a provisional election was made with traverse to prosecute the invention of chimeric protein comprising anti- MHC II binding portion, p53 effector portion and HIV tat translocation portion. Examiner agreed to examiner the elected species expressed in any target cell. Affirmation of this election must be made by applicant in replying to this Office action. The claims are examined as they read upon the elected species, IE a chimeric protein comprising anti- MHC II binding portion, p53 effector portion and HIV tat translocation portion. Claim withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. Applicant is required to amend the specification to disclose SEQ. ID. NO.'s. and to submit a CRF. See Attached sheet.

3. The disclosure is objected to because of the following informalities: The specification should be amended to disclose "BRIEF DESCRIPTION OF THE FIGURES" heading on page 7.

4. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

5. This application lacks the necessary reference to the prior application. A statement reading "This is a of Application No.----filed------- ." should be entered following the title of the invention or as the first sentence of the specification. Also, the current status of all non-provisional parent applications referenced should be included.

6. Claims 1-23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Reasons are set forth below.

A. In claims 1 and 2, line 2, it is unclear what the term "effective portion thereof" means. Is this term limited Fab and $F(ab)_2$ fragments of an immunoglobulin molecule?

B. Claim 2 contains a typographical error. "chemaeric" should be "chimeric".

C. In claim 6, it is unclear what the term "modulate" means. Does this term encompass increasing and decreasing?

D. In claim 9 it is unclear what the term "capable of exerting an immunodulatory effect" means. It is unclear what effects are being referred. Does the claim language encompass immunomodulatory effects which increase and decrease the immune response?

E. In claim 2, it is unclear what the term "exerting a biological effect" means. What biological effects are being referred to? Is the "biological effect" limited to eliciting an immune response to the specific peptide?

F. In claim 1, it is unclear what the metes and bounds of the term "immunogenic peptide" are. What are the maximum and minimum lengths of the peptide? Must the peptide be 9-10 amino

acids long or can the peptide be longer. If so must the peptide be processed to peptide 9-10 amino acid long that is capable of binding to MHC molecules of the targeted cell?

7. Claims 7-23 are objected to under 37 CFR 1.875(c) as being in improper form because a multiple dependent claim cannot be dependent upon another multiple dependent claim, nor can it be co-dependent upon more than one base claim. See MPEP 608.01(n).

Claims 8-14 are objected to because the claim must recite the claims upon which it is dependent in place of the term "according to any one of the preceding claims".

The specification and claims should be amended to use American English, not British English. For instance "chimaeric" should be "chimeric."

8. A chimeric protein comprising anti-MHC II antibody-p53-HIV-TAT is not entitled to benefit of priority documents Great Britain 9409643.8 (filed 5/13/94) or Great Britain 94 17461.2 (filed Aug. 18, 1994) because there is no support for a such a chimeric protein in these priority documents. Is Applicant disagrees, applicant should present a detailed analysis as to why the claimed subject matter has clear support in the specification.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Donnelly et al. EP 0 532 080 A2 (issued Sept. 2, 1992(, and further in view of Zimmerman et al. US 5,652,341 (issued Jul 29, 1997, priority to Dec. 4, 1992) Murphy US 5,668,255 (issued Sep. 16, 1997, priority to Jun 27, 1991), Lowenadler et al. (Mol. Immunology 29:1195, 1992), Fawell et al. (PNAS 91: 1994), Noguchi et al. (PNAS 3171, April 1994) and Roemer et al. PNAS(90:9252, 1993).

EP 0 532 090 A2 teaches chimeric peptides comprising a cellular recognition portion, Pseudomonas exotoxin translocating portion and an immunogenic peptide effector portion (see Claims 1-7 and abstract, in particular). EP 05320909 A2 does not teach a chimeric protein in which the translocating domain is HIV TAT protein.

However, Fawell et al. teach that a chimeric protein comprising HIV TAT protein and β-galactosidase which can deliver heterologous macromolecules into cells such as endothelial cells, Kupffer cells or splenic macrophages (which are APC cells). Therefore it would have been prima facie obvious to one with skill in the art at the time of the invention to substitute the HIV TAT translocation domain for the Pseudomonas translocation domain of the chimeric protein taught by EP 0532 080 A2 with the expectation that such a molecule would deliver the immunogenic peptide to the target cell and that the molecule would be translocated into the cell. Thus these references in combination teach a chimeric protein comprising a cellular recognition domain-- immunogenic peptide-- HIV TAT.

EP 0532080 A2 does not teach that the cellular recognition domain of the chimeric protein is a anti-MHC II antibody or effective binding portion thereof. However, Murphy et al. teach a chimeric polypeptide comprising a translocation region and a cell binding region in which the binding region is an antigen binding portion of an immunoglobulin with specificity to an antigen expressed on a target cell (see abstract and column 3 line 14 through column 4, line 51, in particular). Zimmerman et al. teach a chimeric protein comprising a cellular binding portion and

an antigen associated with a disease or an immunogenic epitope thereof, in which the cellular binding portion is specific for MHC Classes I and II such as beta 2-microglobulin or antibodies to cell surface proteins (see column 4, lines 46-55 , in particular). Therefore it would have obvious to one with skill in the art at the time of the invention to modify the chimeric protein taught by EP 0532080 in view of Fawell et al. by substituting an anti-MHC II immunoglobulin for the cell binding portion taught by EP 0532080 with the expectation that such a chimeric molecule would target MHC II bearing cells, including T cells and APC and that the polypeptide would be translocated into the cell.

Lowenadler et al. teach chimeric proteins comprising cellular binding portion (Ig-G binding domain of protein A), translocation portion (enterotoxin from E. coli) and immunogenic peptides which are repeats of an peptide comprising an immunodominant epitope of ovalbumin linked to an peptide derived from insulin like growth factor (see Figure 1 and abstract in particular). Lowenadler et al. teach that such a chimeric protein which elicits T and B cell responses to the immunogenic peptides (see abstract, Figures 2-3, and pages 1188-1189, in particular).

Therefore it would have been prima facie obvious to one with skill in the art at the time of the invention to modify the chimeric protein taught by the previously cited references to substitute repeats of the same peptide or a polypeptide effector portion comprising a plurality of different peptides for the immunogenic peptide effector portion of the chimeric protein taught by the prior art references with the expectation that such a polypeptide would induce immune responses to the immunogenic peptide effector portion of the chimeric protein.

Romer et al. teach a chimeric protein in which comprises p53 effector portion and human estrogen receptor hormone binding portion. The human estrogen receptor hormone binding portion targets the chimeric protein to cells expressing estrogen receptors. Noguchi et al. teach that p53 is expressed on tumor cells and that CTL specific for p53 may be induced by immunizing with peptides derived from p53. Therefore it would have been prima facie obvious to

one with skill in the art at the time of the invention to substitute p53 or fragments of p53 for the immunogenic peptide effector portion of the chimeric polypeptides taught by the prior art with the expectation that the polypeptide chimeric protein would be targeted to cells such as APC expressing MHC II and that an immune response, including CTL, to p53 would be elicited.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Martha Lubet whose telephone number is (703) 305-7148. The examiner can normally be reached on Monday through Friday from 8:15 AM to 4:45 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (703) 305-3973. The FAX number for this group is (703) 305-3014 or 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Martha T. Lubet

July 31, 1998

TC

THOMAS M. CUNNINGHAM
PRIMARY EXAMINER

Application No. 08/737,457

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

☑ 1. This application clearly fails to comply with the requirements of 37 CFR 1.821 - 1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29 May 15, 1990 and at 55 FR 18230, May 1, 1990. ~~See Office Action~~ Sequences IN SPECIFICATION BUT NO CRF Submitted.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).

☐ 7.

Other: _____

Applicant must provide:

☑ An initial ~~or substitute~~ computer readable form (CRF) copy of the "Sequence Listing"

☑ An initial ~~or substitute~~ paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification

☑ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please contact:

For Rules Interpretation, call (703) 308-1123
For CRF submission help, call (703) 308-4212
For PatentIn software help, call (703) 557-0400

Please return a copy of this notice with your response.